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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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VIKSNINS HARRIS & PADYS PLLP
P.O. BOX 111098
ST. PAUL, MN 55111-1098

EXAMINER	
HUMPHREY, DAVID HAROLD	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 04/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/668,057	SANDLER, ANTHONY D.	
	Examiner	Art Unit	
	David Humphrey	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *19-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/23/06;9/22/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of Group I, claims 1-18, without traverse in the reply filed on 03/16/2006 is acknowledged.

2. Claims 1-21 are pending.

Claims 19-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention/species.

Claims 1-18 are examined on the merits.

Specification

3. Applicant is required to update the status (pending, allowed, etc.) of all parent priority applications in the first line of the specification. The status of all citations of US filed applications in the specification should also be updated where appropriate.

4. The abstract of the disclosure is objected to because it does not clearly describe the invention. The phrase "calculating the ratio of the amount of Survivin **and** the amount of PAF" implies that more than one ratio is calculated. The abstract should be amended to read "the ratio of the amount of Survivin **to** ...". In addition, the abbreviation PAF is not commonly used. Applicant is requested to insert the full name,

"pro-apoptosis factor" prior to citing the abbreviation in the Abstract. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 112, second paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 1 is vague and indefinite for the recitation "effective to hybridize protein". It is unclear how a protein possesses sequence complementarity. Hybridization is useful for determining sequence similarity among DNAs of different origin. One possibility is that the conditions are "effective to bind protein".

b. Claim 1 is vague and indefinite for the recitation "survivin-specific ligand". It is not clear what cytoplasmic protein, receptor, or small molecule binds to survivin to form a larger complex. As evidenced by Altieri (Trends in Molecular Medicine 7(12): 542-547, 2001), survivin binds to microtubules and kinetochore but does not indicate that there is a receptor or other protein that is specific for survivin, see page 542, right column, second complete paragraph, lines 10-19. One possibility is that the survivin-specific ligand is an antibody that binds only to survivin.

c. Claim 1 is vague and indefinite for the recitation "pro-apoptosis factor (PAF) specific ligand". It is not clear what cytoplasmic protein, receptor, or small molecule binds to PAF to form a larger complex.

d. Claims 4-6 are vague and indefinite for the recitation "the PAF". It is not clear whether "the PAF" refers to a PAF-specific ligand or the PAF itself.

e. Claims 7 and 14 recite the limitation "the physiological sample". There is insufficient antecedent basis for this limitation in the claim.

f. Claim 16 recites the limitation "the agent". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112, first paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-18 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied

through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical characteristics and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus. " (See MPEP 2164).

The claims are drawn to method for predicting the recurrence of a tumor or cancer in a mammal comprising calculating the ratio of the amount of Survivin to the amount of pro-apoptosis factor wherein a Survivin:PAF ratio of more than about 1.5 is predictive of tumor recurrence. The method requires the utilization of a Survivin-specific ligand, which encompasses a genus of possible molecules or proteins. The only Survivin-specific ligand disclosed by Applicants is an anti-Survivin antibody. Therefore, the term "Survivin-specific ligand" encompasses any cytoplasmic proteins, receptors, and inorganic molecules, for example, that bind to any Survivin, Survivin variant, Survivin homolog, etc.

The gene and protein name Survivin could encompass homologous sequences in other species, alternative splice variants, allelic variants, untranslated regions, possible enhancer or other regulatory sequences, and sequence mutations. For example, Krieg A. et al. (British Journal of Cancer 86: 737-743, 2002) teach expression of different survivin variants in gastric carcinomas, see article title and abstract. Krieg et al. also teach that one variant, survivin-2B may act as a naturally occurring antagonist of survivin, see page 737, Abstract, lines 2-4. Mahotka C et al. (Cancer Research 59:

6097-6102, 1999) also teach that sequence alterations in the two splice variants of survivin caused marked changes in the structure of the corresponding proteins, inducing structural modifications of the baculovirus inhibitor of apoptosis protein repeat domain, see page 6097, Abstract, lines 14-16. Since the term "Survivin-specific ligand" encompasses any cytoplasmic proteins, receptors, and inorganic molecules, for example, that bind to any Survivin, Survivin variant, Survivin homolog, etc., the claims are directed to a "Survivin-specific ligand" are very broad.

The specification defines the term "Survivin sequence" or other apoptotic inhibitor or pro-apoptotic factor of interest) to include the prepro, pro and mature forms of the apoptotic inhibitor and pro-apoptotic factor of interest as well as subunits of those polypeptides, see page 11, lines 16-19. The specification further discloses that a mature Sruvivin polypeptide, as well as variant Survivin polypeptides which share at least 90% homology with the known Survivin sequence are within the scope of the term "Survivin polypeptide", see page 11, lines 19-22. Since the specification provides a limited definition of Survivin-specific ligand, the claims can encompass any protein, inorganic molecules, antibodies, DNA, or fragments thereof that bind to Survivin, and naturally or even non-naturally occurring modifications of Survivin, e.g. cleavage, glycoslyations, methylations, acetylations, amidations, phosphorylations, sulfatations, deletions, substitutions, etc. The specification provides insufficient written description to support the broad genus of variants encompassed by the claims.

To provide adequate written description and evidence of possession of a claimed genus, Survivin-specific ligands, the specification must provide sufficient distinguishing

identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only species present in the claims is an antibody that binds Survivin. There is no identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Per the Enzo court's example of a description of an anti-inflammatory steroid couched "in terms of its function of lessening inflammation of tissues," which, the court stated, "fails to distinguish any steroid from others having the same activity or function," and which therefore, fails to satisfy the written-description requirement. Similarly, "Survivin" does not distinguish variants or portions thereof from any other amino acid sequence having the same activity or function and as such, does not satisfy the written-description requirement. Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed

above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

9. Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a diagnostic method for predicting the recurrence of a tumor or cancer in a human by quantifying the amount of Survivin protein, does not reasonably provide enablement for a diagnostic method for predicting the recurrence of a tumor or cancer in any mammal by calculating the protein ratio of Survivin to pro-apoptotis factor (PAF) proteins wherein the ratio more than about 1.5 is predictive that the tumor will recur. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir,1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue' not 'experimentation'. " (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of one of ordinary skill, (5) the level of predictability in the art, (6) the amount of direction provided by the inventor, (7) the existence of working examples, (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims and the nature of the invention: The claims are drawn to a diagnostic method for predicting the recurrence of a tumor or cancer in a mammal comprising contacting a mammalian tissue with a Survivin-specific ligand comprising a first label, and a pro-apoptotic factor (PAF)-specific ligand comprising a second label and then quantifying the first and second populations of labeled protein to determine the amount of Survivin and an amount of PAF present in the sample and then calculating the ratio of the amount of Survivin to the amount of PAF, wherein the Survivin:PAF ratio of more than about 1.5 is predictive that the tumor will recur. The PAF protein can be

one the following proteins: Fas, BID, p53, DR4, DR5, TNF-R, or Caspase 8. Claim 11 recites the limitation that the tumor is a childhood tumor selected from the following: Neuroblastoma, Pediatric renal tumor, Hepatoblastoma, Rhabdomyosarcoma, an undifferentiated sarcoma, a germ cell tumor or an endocrine tumor. Claim 13 recites the limitation that the tumor is an adult tumor selected from tumors of the nervous system, of the gastrointestinal or urogenital tract, or a sarcoma. Therefore, the claims encompass tumor recurrence where the subject is any mammal.

The state of the prior art and the level of predictability in the art: Those of skill in the art recognize that expression of mRNA, specific for a tissue type, does not necessarily correlate nor predict equivalent levels of polypeptide expression. In fact, evidence abounds in which protein levels do not correlate with steady-state mRNA levels or alterations in mRNA levels. For example, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Further, Powell et al (Pharmacogenesis, 1998, Vol. 8, pp. 411-421, abstract) teach that mRNA levels for cytochrome P450 E1 did not correlate with the level of corresponding protein, and conclude that the regulation of said protein is highly complex. Vallejo et al (Biochimie, 2000, vol. 82, pp. 1129-1133, abstract) teach that no correlation was found between NRF-2 mRNA and protein levels suggesting post-transcriptional regulation of NRF-2 protein levels. These references serve to demonstrate that the analysis of levels of polynucleotide transcripts cannot be relied upon to anticipate levels of protein

expression. Further, Jang et al (Clinical and Experimental Metastasis, 1997, vol. 15, pp. 469-483, abstract) teach that further studies are necessary to determine if changes in protein levels track with changes in mRNA levels for metastasis associated genes in murine tumor cells, thus providing further evidence that one of skill in the art cannot anticipate that the level of a specific mRNA expressed by a cell will be paralleled at the protein level due to complex homeostatic factors controlling translation and post-translational modification.

Thus, the predictability of protein translation and its possible utility as a diagnostic are not necessarily contingent on the levels of mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. Therefore, absent evidence of the protein's expression including the correlation to a diseased state, one of skill in the art would be unable to predictably use the polypeptides in any diagnostic setting without undue experimentation.

In addition, the breadth of the claims is considered to encompass any and all mammals, be they marine life, egg-laying mammals, marsupials, equines, etc. Given the tremendous differences in physiological systems, undoubted differences in genetic composition, and the non-disclosure of the relevant antibodies required to bind to the relevant proteins, a greater level of disclosure is required

The amount of direction provided by the inventor and the existence of working examples: There are no working examples in the specification that are commensurate in scope with the claimed invention. Examples 1-5 quantify the mRNA expression levels using the Rnase Protection Assay and the Survivin:PAF ratios disclosed were

calculated from mRNA expression levels. There is no quantitation of PAF proteins by antibodies and labels. The specification only describes Western blot and immunohistochemical analysis of Survivin protein. Since no PAF protein levels have been quantified, and in view of the prior art that states that mRNA levels do not necessarily reflect protein expression levels, one of ordinary skill would be required undue experimentation to determine the protein ratios which predict tumor recurrence. Applicant has also only provided measurement of survivin levels in humans which is not enabling for any and all mammals.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed inventions without undue experimentation. In re Wright, 27 USPQ2d 1510 (CAFC). The disclosure does not demonstrate sufficient evidence to support Applicant' claim to a diagnostic method for predicting tumor recurrence using the ratio of Survivin:PAF protein. All of the factors considered in the sections above, underscores the criticality of providing working examples in the specification for an unpredictable art such as providing gene therapy to animals to treating cardiovascular diseases.

Quantity of experimentation needed to make or use the invention based on the content of the disclosure: In view of the Wands factors considered above, one of ordinary skill in the art would conclude that claim to a diagnostic method for predicting tumor recurrence using the ratio of Survivin:PAF protein would require undue experimentation in order to practice the invention as claimed by the Applicant.

10. NOTE: In view of the fact that the disclosure is enabling for the determining the levels of Survivin protein in a human sample, the following art rejection is applied.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. Claims 1-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lu D et al. (Cancer Research 58: 1808-1812, 1998) in view of LaCasse EC et al. (Oncogene 17: 3247-3259, 1998), Adida C et al. (The Lancet 351: 882-883, 1998), and Tamm et al. (Cancer Research 58: 5315-5320, 1998).

While the claims are drawn to a diagnostic method for predicting the recurrence of a tumor in a mammal comprising contacting a tissue sample suspected of being tumorigenic with a Survivin-specific ligand and a pro-apoptosis factor (PAF)-specific ligand, quantifying the amount of Survivin and the amount of PAF, they are only partially enabled, see enablement rejection above. Claims 4-6 recite the method wherein the PAF is Fas, BID, p53, DR4, DR5, TNF-R, or caspase 8. Claims 7-15 recite the method wherein the sample is a tissue sample, tissue-lysate protein sample, solid tumor, childhood tumor selected from a group of tumors, an adult tumor selected from a group of tumors, or a fluid sample that is whole blood or blood serum. Clams 16-18 recite the method wherein the ligand is an antibody.

Lu D et al. teach the immunohistological testing of gastric cancer cells for survivin protein levels using an anti-survivin antibody, see page 1810, left column, lines 13-18. Lu et al. further teach measuring the expression of p53 in the same tumor samples using anti-p53 antibodies and that survivin protein levels were higher in p53-positive tumor cells, see page 1810, right column, lines 6-12 and page 1811, Figure 3. Lu et al. teach that apoptotic index was inversely correlated with increased survivin expression, see page 1811, left column, lines 1-6, and figure 3b, and Table 2. Lu does not teach surviving levels in childhood tumors such as neuroblastoma. This deficiency is made up for by the teachings of LaCasse EC et al. and Adida C et al.

LaCasse EC et al. (Oncogene 17: 3247-3259, 1998) teach that survivin is expressed in most cancers tested (lung, colon, breast, prostate, pancreas, high grade lymphomas, neuroblastomas, and gastric), see page 3256, left column, second

complete paragraph, lines 11-16. LaCasse et al. teach that survivin has been shown to protect against apoptosis, see page 3256, bottom of the left column, last sentence bridging to the right column.

Adida C et al. (The Lancet 351: 882-883, 1998) teach that the increased levels of survivin protein as determined by immunohistochemistry and immunoblotting segregated with unfavorable histology, see page 882, right column, second complete paragraph, lines 1-3 and lines 6-10. Adida et al. teach that the survivin protein correlates with a more aggressive and histologically unfavorable disease and could therefore serve as a predictive factor in neuroblastoma, see page 883, left column, first complete paragraph, lines 1-4. Lu et al., LaCasse et al., and Adida et al. do not teach that increased levels of survivin inhibits specific proapoptotic factors. This deficiency is made up for by the teachings of Tamm et al.

Tamm et al. (Cancer Research 58: 5315-5320, 1998) teach that survivin inhibits caspase activity and apoptosis induced by Fas, Bax, caspases (including caspase-8), and anticancer drugs, see page 5315, article title and Abstract, lines 4-10, and lines 16-18.

It would have been *prima facie* obvious for one of ordinary skill in the art at the time the claimed invention was made to combine the teachings of Lu et al., LaCasse et al., Adida et al. and Tamm et al. for produce a diagnostic method for predicting the recurrence of a tumor. One would have been motivated with a reasonable expectation of success since Adida et al. teach that the survivin protein correlates with a more aggressive and histologically unfavorable disease and could therefore serve as a

predictive factor in neuroblastoma and Tamm et al. teach that survivin inhibits the activity of caspases and apoptosis induced by Fas.

Thus, claims 1-18 are obvious over Lu et al., in view of LaCasse et al, Adida et al., and Tamm et al.

Conclusion

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Humphrey whose telephone number is (571) 272-5544. The examiner can normally be reached on Mon-Fri 8:30AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David Humphrey, Ph.D.

April 14, 2006